Radiotherapy in metastatic spinal cord compression: a review of fractionation

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SUMMARY

Metastatic spinal cord compression, a term normally including compression of the spinal cord or nerve roots running within the spinal canal, is a common complication of systemic cancer, occurring in 5–10% of all patients with cancer. Recent published data on treatment of metastatic spinal cord compression (MSCC) have shown that radiotherapy (RT) alone is an effective approach for the majority of cases. Except for some protocols, the use of conventional RT (daily fractions of 2 Gy to a total dose of 30–40 Gy) has been abandoned in favour of radiation treatment regimens requiring a smaller number of fractions. In some published trials, 4–5 Gy daily for 8 days followed by 4 days rest, and then 5–16 daily doses of 2–3 Gy have been given with both good results and tolerance. Higher daily fractions ranging from 6 to 10 Gy have also been explored with similar results.
We have summarized the studies comparing the treatments and clinical outcome. Most patients with MSCC have a life expectancy of only several months. In these patients one radiotherapeutic schedule with a short overall treatment time would be the best option, if its effect on the most relevant clinical symptoms, pain and motor dysfunction, is comparable to the effect of more protracted schedules. In patients with a reduced life expectancy, a radiotherapeutic effect on recalcification, which can be expected only several months after RT, is of minor importance. In patients with a life expectancy of more than a few months, recalcification becomes more of an issue and a more fractionated radiation schedule should be considered.

KEY WORDS: metastatic spinal cord compression, radiotherapy, fractionation, response, toxicity

INTRODUCTION

Metastatic spinal cord compression, a term normally including compression of the spinal cord or nerve roots running within the spinal canal, is a common complication of systemic cancer, occurring in 5-10% of all patients with cancer. The prognosis is influenced by many factors, and large retrospective studies comprising more than 150 patients as well as studies comprising fewer patients have tried to evaluate the prognostic significance of different clinical and radiological variables present at the time of diagnosis. Both prospective and retrospective studies agree that the most effective management of an epidural metastasis is to initiate treatment before neurological deficits develop.

Surgery (i.e. compressive laminectomy) plus radiotherapy (RT) or RT alone are both good strategies, provided they are performed early. Because the success of treatment is related to the severity of the epidural disease and clinical condition at the time of diagnosis, it is important to perform diagnosis early and to begin treatment before significant myelopathy develops. A tendency to prefer RT rather than surgery has emerged over the last years in view of its greater feasibility. In fact, surgery results in 3–14% mortality and 5–30% morbidity rate and the wound confines the patients to bed for a certain period. Generally, laminectomy does not remove the neoplastic mass and, when there is vertebral body collapse, it may also cause post-surgery spinal instability. Recent trials indicate that simple laminectomy should be abandoned in favour of a more aggressive approach (i.e. posterior, anterior, or lateral decompression, plus stabilization of the spine). This special complex technique is advised in selected cases as follows: (a) if there are diagnostic doubts; (b) if stabilization is necessary; (c) if

RT has already been given in the same area; (d) when vertebral body collapse causes bone impingement on the cord or nerve roots. In all other cases RT alone can give the same results as surgery plus RT, and it does not cause remarkable morbidity.

Recent published data on treatment of metastatic spinal cord compression (MSCC) have shown that radiotherapy (RT) alone is an effective approach for the majority of cases. Nevertheless, the optimal radiation schedule is unknown [3]. Except for some protocols, the use of conventional RT (daily fractions of 2 Gy to a total dose of 30 – 40 Gy) has been abandoned in favour of radiation treatment regimens requiring a smaller number of fractions. In some published trials, 4 – 5 Gy daily for 8 days followed by 4 days rest, and then 5 – 16 daily doses of 2 – 3 Gy have been given with both good results and tolerance. Higher daily fractions ranging from 6 to 10 Gy have also been explored with similar results. The purpose of this review was to assess the clinical outcome and toxicity of various fractionated regimes in MSCC.

Fractionation for radiotherapy of MSCC:

Rades et al. (2002) investigated the prognostic value of the time of motor deficit development before radiotherapy (RT). Ninety-eight patients were included between November 1998 and April 2000. Three subgroups were formed, according to time of motor deficit development before RT: 1 – 7 days (n = 31), 8 – 14 days (n=31) and > 14 days (n = 36). Ambulatory rates and motor function were evaluated for < 24 weeks after RT. In a multivariate analysis, all three prognostic factors and radiation parameters were included. In the > 14 days subgroup, improvement occurred significantly ($p < 0.001$) more often than in the other subgroups (86% vs 29% and 10%) and the post-treatment ambulatory rate was significantly higher (86% vs. 55% and 35%, $p = 0.026$). Multivariate analysis revealed the time of development of motor deficits before RT to be the strongest prognostic factor. Functional outcome is significantly better with slower development of motor deficits before RT. This new, independent prognostic factor must be considered in future trials aiming to define an optimal RT schedule.

Larsen et al. (2000) analyzed the prognostic significance of various clinical and radiological variables on post-treatment ambulatory function and survival. During a 3½ year period they prospectively included 153 consecutive patients with a diagnosis of spinal cord compression due to metastatic disease. The patients were followed with regular neurological examinations by the same neurologist for a minimum period of 11 months or until death. The prognostic significance of five variables on gait function and survival time after treatment was analyzed. The type of the primary tumour had a direct influence on the interval between the diagnosis of the primary malignancy and the occurrence of spinal cord compression ($p < 0.0005$), and on the ambulatory function at time of diagnosis ($p = 0.016$). There was a clear correlation between the degree of myelographic blockage and gait function and sensory disturbances ($p = 0.000$). The final gait was dependent on the gait function at time of diagnosis ($p < 0.0005$). Survival time after diagnosis depended directly on the time from primary tumour diagnosis until spinal cord compression ($p = 0.002$), on the ambulatory function at the time of diagnosis ($p=0.018$), and on the ambulatory function after treatment. The pretreatment ambulatory function is the main determinant for post-treatment gait function. Survival time is rather short, especially in non-ambulatory patients, and can only be improved by restoration of gait function in non-ambulatory patients by immediate treatment.

Leviov et al. (1993) performed a retrospective analysis of 70 patients with this complication treated from 1985 to 1989. The most frequent primary diagnoses in their series were carcinomas of unknown origin and of the breast, lymphoproliferative disease, lung cancer, and prostatic carcinoma. They used the Findlay classification to group all patients according to their pre-therapeutic functional motor status as Grade I (24 patients or 34%), grade II (27 or 39%) or grade III (19 or 27%). Treatment consisted of 30–45 Gy of irradiation (using two different schedules) together with high dose dexamethasone; in only five cases was there surgical intervention. They found that a powerful predictor of response to radiotherapy was the patient's neurological status

(Findlay grade) at the time of diagnosis: 66% of previously ambulatory patients remained so, whereas 30% of non-ambulatory patients and only 16% of paraplegic patients regained the ability to walk. Another important predictor of response was primary tumour histology, with the most favourable responses to radiation therapy having been observed in lymphoproliferative diseases and in breast cancer, but with some response in other radiosensitive malignancies as well. The similarity of their results to those of other centres led them to conclude that a radiotherapeutic success ceiling of 80% may have been reached for Findlay Grade I patients with metastatic spinal cord compression. In view of this, they suggested that future therapeutic endeavour would be best directed toward early diagnosis of the condition.

Maranzano and Latini (1995) performed a prospective trial in which patients with this complication were generally treated with RT plus steroids and surgery was reserved for selected cases. Two hundred and seventy-five consecutive patients with MSCC entered this protocol. Twenty (7%) underwent surgery plus RT, and another 255 received RT alone. Of all eligible patients, 25 (10%) early deaths and 21 (8%) entering a feasibility study of RT without steroids were not evaluable. Of the 209 evaluable cases, 110 were females and 99 males and median age was 62 years. Median follow-up was 49 months (range, 13 to 88) and treatment consisted of 30 Gy RT (using two different schedules) together with steroids (standard or high doses, depending on motor deficit severity). Response was assessed according to back pain and motor and bladder function before and after therapy. Back pain total response rate was 82% (complete or partial response or stable pain, 54, 17 or 11%, respectively). About three-fourths of the patients (76%) achieved full recovery or preservation of walking ability and 44% with sphincter dysfunction improved. Early diagnosis was the most important response predictor so that a large majority of patients able to walk and with good bladder function maintained these capacities. When diagnosis was late, tumours with favourable histologies (i.e. myeloma, breast and prostate carcinomas) above all responded to RT. Duration of response was also influenced by histology. Favourable histologies are associated with higher median response (myeloma, breast and prostate carcinomas, 16, 12 and 10 months, respectively). Median survival time was 6 months, with a 28% probability of survival for 1 year. Survival time was longer for patients able to walk before and/or after RT, those with favourable histologies and females. There was agreement between patient survival and duration of response, systemic relapse of disease being generally the cause of death. Early diagnosis of MSCC was a powerful predictor of outcome. Primary tumour histology had weight only when patients were non-walking, paraplegic or had bladder dysfunction. The effectiveness of RT plus steroids in MSCC emerged in their trial. The most important factors positively conditioning their results were: the high rate of early diagnoses (52%) and the number of tumours with favourable histologies (124 out of 209, 63%) recruited and the choice of best treatment based on appropriate patient selection for surgery and RT or RT alone.

Maranzano et al. (1997) evaluated the clinical outcome and toxicity of a short-course regimen of radiotherapy (RT) in selected metastatic spinal cord compression (MSCC) patients. Between 1993 and 1995, 53 consecutive patients with MSCC from low radio-responsive primary tumours (non-small cell lung, kidney, head and neck and gastrointestinal carcinomas, melanoma and sarcomas) or more radioresponsive ones (breast and prostate carcinomas, myeloma and lymphomas) with paresis, plegia, low performance status (PS ECOG ≥ 2) and/or short life expectation, underwent short-course RT: a single fraction of 8 Gy repeated after 1 week in responders or stable patients, for a total dose of 16 Gy. Of 49 (92%) evaluable cases, 4 (8%) underwent surgery plus RT and the other 45 RT alone. Medium doses of parenteral dexamethasone (8 mg x 2/d) were given in all cases and precautionary anti-emetics to those treated with fields covering the upper abdomen (20 of 49 cases). Median follow-up was 25 months (range, 6–34). Response was assessed according to back pain and motor and bladder capacity before and after RT. Pain relief was achieved in 67% of patients and motor function response rate reached 63%. Early diagnosis and therapy were very important in

predicting response to RT; all but two (91%) pretreatment walking patients and all but one (98%) with good bladder function preserved these capacities. In contrast, when diagnosis was late, only 38% of non-ambulatory patients and 44% of those with bladder retention improved. Median survival was 5 months, with a 30% probability of survival for 1 year. Length of survival was significantly longer for patients able to walk before and/or after RT. Good agreement between survival and duration of response was found with no evidence of relapse in the irradiated spine. Sickness appeared only in a few cases. Slight oesophagitis was more frequent: dysphagia for solid foods in one-third of patients irradiated on the thoracic spine. Late toxicity was never recorded. The short-course RT adopted gave a clinical outcome comparable with that resulting from more protracted regimens with only slight side effects. The use of a few large treatment fractions could be explored considering the associated advantages for patients and radiotherapy centres often overloaded by long patient waiting lists.

Maranzano et al. (2005) planned a randomized trial to assess the clinical outcome and toxicity of two different hypofractionated RT regimens in MSCC. Three hundred patients with MSCC were randomly assigned to short-course RT (8 Gy x 2 days) or to split-course RT (5 Gy x 3; 3 Gy x 5). Only patients with a short life expectancy entered the protocol. Median follow-up was 33 months (range, 4 to 61 months). A total of 276 (92%) patients were assessable: 142 (51%) treated with the short-course and 134 (49%) treated with the split-course RT regimen. There was no significant difference in response, duration of response, survival or toxicity found between the two arms. When short- versus split-course regimens were compared, after RT 56% and 59% of patients had back pain relief, 68% and 71% were able to walk and 90% and 89% had good bladder function, respectively. Median survival was 4 months and median duration of improvement was 3.5 months for both arms. Toxicity was equally distributed between the two arms: grade 3 oesophagitis or pharyngitis was registered in four patients (1.5%), grade 3 diarrhoea occurred in four patients (1.5%) and grade 3 vomiting or nausea occurred in 10 patients (6%). Late toxicity was never recorded. Both hypofractionated RT schedules adopted were effective and had acceptable toxicity. However, considering the advantages of the short-course regimen in terms of patient convenience and machine time, it could become the RT regimen of choice in clinical practice for MSCC patients.

Rades (2002) compared three different schedules for functional outcome. For post-treatment functional and ambulatory outcome, three schedules, 30 Gy in 10 fractions (n = 93), 37.5 Gy in 15 fractions (n = 80) and 40 Gy in 20 fractions (n = 74), were compared. Motor function was evaluated on a 6-point scale before and at the end of RT and 3, 6 and 12 months later. A multivariate analysis was performed for functional outcome, including fractionation schedule and the three relevant prognostic factors (primary tumour type, time of developing motor deficits before RT and ambulatory status). No significant difference was observed for post-treatment motor function or ambulatory rates among the three schedules. According to the multivariate analysis, the radiation schedule had no significant impact on functional outcome ($p = 0.223$) in contrast to the three prognostic factors ($p < 0.001$, $p < 0.001$ and $p = 0.012$). The three fractionation schedules were comparable for functional outcome. The least time-consuming schedule (30 Gy in 10 fractions) should be considered for patients with a markedly reduced life expectancy.

Rades et al. (2005) investigated a reduction of the overall treatment time to only one day by comparing 1 x 8 Gy in multi-fractionated 10 x 3 Gy for functional outcome. Data of 204 patients, treated for MSCC with either 1 x 8 Gy (n = 96) or 10 x 3 (n = 108), were analyzed retrospectively. Motor function and ambulatory status were evaluated before and up to 24 weeks after RT. A multivariate analysis (nominal regression) was performed including radiation schedule, performance status, age, irradiated vertebra and relevant prognostic factors (histology, ambulatory status, time of developing motor deficits). Improvement of motor deficits was selected as the basic category and compared with no change and deterioration. Univariate analysis showed no significant difference between the schedules for

post-treatment motor function and ambulatory rates. Multivariate analysis demonstrated a significant effect on functional outcome for the prognostic factors, but not for the radiation schedule (p = 0.853 for no change, p = 0.237 for deterioration). Their data suggested the two fractionation schedules to be comparably effective for functional outcome. Thus, 1 x 8 Gy should be considered for patients with a poor survival prognosis.

Rades et al. (2005) investigated the feasibility and effectiveness of re-irradiation (re-RT) for in-field recurrence of metastatic spinal cord compression after primary RT with 1 x 8 Gy or 5 x 4 Gy. A total of 62 patients, treated with 1 x 8 Gy (n = 34) or 5 x 4 Gy (n = 28) between January 1995 and August 2003, received re-RT for in-field recurrence of metastatic spinal cord compression. The median time to recurrence was 6 months (range, 2-40 months). Re-RT was performed with 1 x 8 Gy (after 1 x 8 Gy or 5 x 4 Gy, n = 34), 5 x 3 Gy (after 1 x 8 Gy or 5 x 4 Gy, n = 15) or 5 x 4 Gy (after 1 x 8 Gy, n = 13). The cumulative biologically effective dose (primary RT plus re-RT) was 80-100 Gy2. The median follow-up after re-RT was 8 months (range, 2-42 months). Motor function was evaluated up to 6 months after re-RT. After re-RT, 25 patients (40%) showed improved motor function, 28 (45%) had no change and 9 (15%) had deterioration. Of the 16 previously non-ambulatory patients, 6 (38%) regained the ability to walk. No second in-field recurrence in the same spinal region was observed after re-RT. The outcome was not significantly influenced by the radiation schedule. Radiation myelopathy was not observed. Spinal re-RT with 1 x 8 Gy, 5 x 3 Gy or 5 x 4 Gy for in-field recurrence of metastatic spinal cord compression appears safe and effective. Myelopathy seems unlikely, if the cumulative biologically effective dose is ≤ 100 Gy2.

CONCLUSION

The concept that RT alone could be the initial treatment for the majority of MSCC patients

Table 1. A review of studies comparing treatments with clinical outcome

Author	Steroids	RT fractionation	Response (%)			Median survival months	Median response months
			Back Pain	Motor dysfunction	Bladder dysfunction		
Maranzano (1995)	Methylpred nisolone 1g/day Dexametha sone 16 mg/d	5 Gy x 3 4 day rest 3 Gy x 5	82	76	44	6	8
Maranzano (1997)	Dexamatha sone 8 mg x 2/d	8 Gy x 1 1 wk rest 8 Gy x 1	67	63	44	5	7
Maranzano (2005)	Dexametha sone 8 mg x 2/d	8 Gy x 1 1 Wk rest 8 Gy x 1	56	68	90	4	3.5
		5 Gy x 3 4 day rest 3 Gy x 5	59	71	89	4	3.5
Rades (2002)	Dexametha sone	30 Gy/ 10 Fr 37.5 Gy/ 15 Fr. 40 Gy / 5 Fr		55 61 56			
Rades (2005)	Dexametha sone	8 Gy x 1 3 Gy x 10		45 41			

is largely accepted. However, tailored surgery (laminectomy or more often decompression and stabilization of the spine) plus RT must be performed in selected cases. With the exception of a few protocols, the use of conventional RT (daily fractions of 2 Gy to a total dose of 30–40 Gy) has been abandoned in favour of RT regimens requiring a few or a number of fractions. Most patients with MSCC have a life expectancy of only several months. In these patients one radiotherapeutic schedule with a short overall treatment time would be the best option, if its effect on the most relevant clinical symptoms, pain and motor dysfunction, is comparable to the effect of more protracted schedules. In patients with a reduced life expectancy, a radiotherapeutic effect on recalcification, which can be expected only several months after RT, is of minor importance. In patients with a life expectancy of more than a few months, recalcification becomes more of an issue and a more fractionated radiation schedule should be considered.

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